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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 4 MAY 1995 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), _____ ~~days~~ from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☒ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☒ Claims 1-34 are pending in the application.
   Of the above, claims 32-34 are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1-31 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☒ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1804. In addition, the first named applicant is Isabelle Riviere, not Mulligan.

Applicant's election with traverse of Group I, claims 1-31, in Paper No. 8, received 4 May 1995 is acknowledged. The traversal is on the ground(s) that the restriction is "improper because Groups II and III both recite logical applications/methods for using the claimed retroviral vectors, and are exemplary of some [of] the therapeutic uses contemplated for the subject vectors. This is not found persuasive because the "logical applications/methods" of use are distinct for the reasons as set forth in the previous office action and are drawn to different inventions. Applicant is also reminded that a search of the relevant literature is directed to art which would anticipate or render obvious each claimed invention. In addition, a search of the art for considerations of enablement under 35 U.S.C. § 112, first paragraph, is required. As such the search of the additional inventions would require an undue burden.

The requirement is still deemed proper and is therefore made FINAL.

Claims 32-34 are withdrawn from further consideration by the examiner, 37 C.F.R. § 1.142(b), as being drawn to a non-elected invention, the requirement having been traversed in Paper No. 8.

35 U.S.C. § 101 reads as follows:

"Whoever invents or discovers any new and useful process, machine, manufacture, or

composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

Claims 5, 6 and 15 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 24, 6 and 15 of copending application Serial No. 07/786,015. This is a *provisional* double patenting rejection since the conflicting claims have not in fact been patented.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 5, 6 and 15 are provisionally rejected under 35 U.S.C. 102(e) as being anticipated by copending application Serial No. 07/786,015 which has a common inventor with the instant application.

Based upon the earlier effective U.S. filing date of the copending application, it would constitute prior art under 35 U.S.C. 102(e) if patented. This provisional rejection under 35 U.S.C. 102(e) is based upon a presumption of future patenting of the copending application.

Claims 5, 6 and 15 are drawn to general and specific vectors which are identical to those

claimed in the copending application.

This provisional rejection under Section 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the copending application was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Claims 5, 6 and 15 are directed to the same invention as that of claims 24, 6 and 15 of commonly assigned copending application Serial No. 07/786,015. The issue of priority under 35 U.S.C. 102(g) and possibly 35 U.S.C. 102(f) of this single invention must be resolved.

Since the Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP § 2302), the assignee is required to state which entity is the prior inventor of the conflicting subject matter. A terminal disclaimer has no effect in this situation since the basis for refusing more than one patent is priority of invention under 35 U.S.C. 102(f) or (g) and not an extension of monopoly.

Failure to comply with this requirement will result in a holding of abandonment of the application.

Claims 5, 6 and 15 of this application conflict with claims 24, 6 and 15 of application serial number 07/786,015. 37 C.F.R. § 1.78(b) provides that when two or more applications filed by the same applicant contain conflicting claims, elimination of such claims from all but one application may be required in the absence of good and sufficient reason for their retention during pendency in more than one application. Applicant is required to either cancel the conflicting claims from all but one application or maintain a clear line of demarcation between the applications. See M.P.E.P. § 822.

The non-statutory double patenting rejection, whether of the obvious-type or non-obvious-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in

the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornam*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); and *In re Goodman*, 29 USPQ2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321 (b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.78 (d).

Effective January 1, 1994, a registered attorney or agent of record may sign a Terminal Disclaimer. A Terminal Disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-4, 7-14 and 16-22 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 7-14 and 16-23 of copending application Serial No. 07/786,015. Although the conflicting claims are not identical, they are not patentably distinct from each other because the vectors and packaging cells claimed in the copending application contain essentially the same components and as those claimed in the instant application. The differences lie in the particular gene inserted in the vector, i.e. whether or not it encodes a selectable marker. Such constructs would have been obvious variations on the vectors of the copending application.

This is a *provisional* obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 23-31 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 21-24, 7-14, 16-20 of

copending application Serial No. 07/786,015 in view of Hilberg et al. [Proc. Natl. Acad. Sci. USA **84**:5232-5236 (1987)], Holland et al. [Proc. Natl. Acad. Sci. USA **84**:8662-8666 (1987)], Franz et al. [Proc. Natl. Acad. Sci. USA **83**:3292-3296 (1986)] and Weiher et al. [Journal of Virology **61(9)**:2742-2746 (1986)].

The copending application teaches the construction and use of retroviral vectors derived from a murine leukemia virus; the vectors do not contain a complete *gag*, *env* or *pol* gene. These vectors can encode a gene of interest, which may or may not encode a selectable marker. In addition, the vectors may contain an exogenous enhancer sequence from another virus.

Regarding claim 23, Hilberg et al. [Proc. Natl. Acad. Sci. USA **84**:5232-5236 (1987)] teaches that retroviral vectors based upon Moloney murine leukemia virus (MuLV) may be generated which contain the enhancer region from myeloproliferative sarcoma virus (MPSV) mutant. Substitution of this enhancer for the exogenous enhancer of the vectors in the copending application would have been obvious, especially in view of the teaching that the use of the MPSV enhancer allows expression of the viral vector genome in embryonal carcinoma cells, a developmental cell line.

Regarding claim 24, Holland et al. [Proc. Natl. Acad. Sci. USA **84**:8662-8666 (1987)] teaches that retroviral vectors based upon Moloney murine leukemia virus (MuLV) may be generated which contain the enhancer region from Friend murine leukemia virus (Fr-MuLV). Substitution of this enhancer for the exogenous enhancer of the vectors in the copending application would have been obvious, especially in view of the teaching that the use of the (Fr-

MuLV) enhancer allows expression of the viral vector genome in hematopoietic progenitor cells.

Regarding claims 25, 27, 29 and 31, Weiher et al. [Journal of Virology **61(9)**:2742-2746 (1986)] teach that the B2 mutation of MuLV vectors works synergistically with the enhancer element and allows for enhanced RNA stability in certain cells, such as F9 cells. The discussion suggests that the B2 mutation may affect the efficiency of translation as well. Inclusion of the B2 mutation in the vectors of the copending application would have been obvious as a means of increasing gene expression in these vectors.

Regarding claims 26-31, Franz et al. [Proc. Natl. Acad. Sci. USA **83**:3292-3296 (1986)] teaches that retroviral vectors using MPSV LTRs can result in expanded host range of the vectors, especially in efficient transduction of embryonic cells. Inclusion of these LTR elements would have been obvious as a means of increasing the host range of the MuLV based vectors.

The combined teachings of the prior art suggest alternative enhancer elements, LTRs or the B2 mutation as further improvements to retroviral vectors. These substitutions for vector sequences can increase gene expression or provide for efficient gene expression in certain cell types that normally are refractive to gene expression using MuLV-based vectors. Applicant's use of these elements in the vectors as claimed would have been obvious given these teachings.

This is a *provisional* obviousness-type double patenting rejection.

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject

matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 1-4, 7-14 and 16-22 are provisionally rejected under 35 U.S.C. § 103 as being obvious over copending application Serial No. 07/786,015.

Copending application Serial No. 07/786,015 has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the copending application, it would constitute prior art under 35 U.S.C. § 102(e) if patented. This provisional rejection under 35 U.S.C. § 103 is based upon a presumption of future patenting of the conflicting application.

This provisional rejection might be overcome either by a showing under 37 C.F.R. § 1.132 that any unclaimed invention disclosed in the copending application was derived from the inventor of this application and is thus not the invention "by another", or by a showing of a date of invention prior to the effective U.S. filing date of the copending application under 37 C.F.R. § 1.131.

The copending application discloses essentially the same vectors and packaging cells

transduced with these vectors as those claimed in claims 1-4, 7-14 and 16-22 of the instant application. The claims of the instant application are not limited to vectors which do not contain a gene encoding a selectable marker. The disclosure of the copending application, however, teaches such vectors.

Claims 23-31 are provisionally rejected under 35 U.S.C. § 103 as being obvious over copending application Serial No. 07/786,015 taken in view of Hilberg et al. [Proc. Natl. Acad. Sci. USA **84**:5232-5236 (1987)], Holland et al. [Proc. Natl. Acad. Sci. USA **84**:8662-8666 (1987)], Franz et al. [Proc. Natl. Acad. Sci. USA **83**:3292-3296 (1986)] and Weiher et al. [Journal of Virology **61(9)**:2742-2746 (1986)].

Copending application Serial No. 07/786,015 has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the copending application, it would constitute prior art under 35 U.S.C. § 102(e) if patented. This provisional rejection under 35 U.S.C. § 103 is based upon a presumption of future patenting of the conflicting application.

This provisional rejection might be overcome either by a showing under 37 C.F.R. § 1.132 that any unclaimed invention disclosed in the copending application was derived from the inventor of this application and is thus not the invention "by another", or by a showing of a date of invention prior to the effective U.S. filing date of the copending application under 37 C.F.R. § 1.131.

The disclosure of the copending application is described *supra*. In addition, Hilberg et al. [Proc. Natl. Acad. Sci. USA **84**:5232-5236 (1987)], Holland et al. [Proc. Natl. Acad. Sci. USA **84**:8662-8666 (1987)], Franz et al. [Proc. Natl. Acad. Sci. USA **83**:3292-3296 (1986)] and Weiher et al. [Journal of Virology **61(9)**:2742-2746 (1986)] are also described *supra*. For

essentially the same reasons as set forth *supra*, the combined teachings of the prior art suggests the modification of murine leukemia virus based vectors to increase gene expression or provide for efficient gene expression in certain cell types that normally are refractive to gene expression using MuLV-based vectors. Applicant's use of these elements in the vectors as claimed would have been obvious given these teachings.

Claims 1-4, 7-14 and 16-22 are directed to an invention not patentably distinct from claims 7-14 and 16-23 of commonly assigned application Serial No. 07/786,015.

Specifically, the claims of the copending application are directed to retroviral vectors derived from a murine leukemia virus; the vectors do not contain a complete *gag*, *env* or *pol* gene. These vectors can encode a gene of interest, but all vectors claimed do not encode a marker. In addition, the vectors may contain an exogenous enhancer sequence from another virus. Claims drawn to packaging cell lines transduced with these vectors are also in the copending application. The claims in the instant application are somewhat broader in that the gene of interest is not limited and may or may not contain a gene encoding a selectable marker.

Claims 23-31 are directed to an invention not patentably distinct from claims 7-14 and 16-23 of commonly assigned application Serial No. 07/786,015 in view of Hilberg et al. [Proc. Natl. Acad. Sci. USA **84**:5232-5236 (1987)], Holland et al. [Proc. Natl. Acad. Sci. USA **84**:8662-8666 (1987)], Franz et al. [Proc. Natl. Acad. Sci. USA **83**:3292-3296 (1986)] and Weiher et al. [Journal of Virology **61(9)**:2742-2746 (1986)].

Specifically, claims 7-14 and 16-23 are described *supra*. Hilberg et al. [Proc. Natl. Acad.

Sci. USA **84**:5232-5236 (1987)], Holland et al. [Proc. Natl. Acad. Sci. USA **84**:8662-8666 (1987)], Franz et al. [Proc. Natl. Acad. Sci. USA **83**:3292-3296 (1986)] and Weiher et al. [Journal of Virology **61(9)**:2742-2746 (1986)] are also described *supra*. For essentially the same reasons as set forth *supra*, the combined teachings of the prior art suggests the modification of murine leukemia virus based vectors to increase gene expression or provide for efficient gene expression in certain cell types that normally are refractive to gene expression using MuLV-based vectors. Applicant's use of these elements in the vectors as claimed would have been obvious given these teachings.

Commonly assigned application Serial No. 07/786,015, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. § 103 if the commonly assigned case qualifies as prior art under 35 U.S.C. § 102(f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee is required under 37 C.F.R. § 1.78(c) to either show that the conflicting inventions were commonly owned at the time the invention in this application was made or to name the prior inventor of the conflicting subject matter. Failure to comply with this requirement will result in a holding of abandonment of the application. A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. § 103 based upon the commonly assigned case as a reference under 35 U.S.C. § 102(f) or (g).

Claims 1, 7, 8, 20 and 21 are rejected under 35 U.S.C. § 102(b) as being anticipated by

Temin [in *Gene Transfer*, R. Kucherlapati (Ed.), Plenum Press, N.Y., pp. 149-187, (1986)].

Temin teaches the construction of various defective recombinant retroviral vectors based on murine leukemia viruses. These vectors can express a gene of interest. At page 163, the reference notes that there "are no reports of genes that cannot be expressed in retrovirus vectors." Helper cells transduced with these vectors are taught on page 156. These vectors and cells anticipate applicant's claimed vectors and cells.

Claims 2, 3, 4 and 20 are rejected under 35 U.S.C. § 103 as being unpatentable over Temin [in *Gene Transfer*, R. Kucherlapati (Ed.), Plenum Press, N.Y., pp. 149-187, (1986)] and Bender et al. [J. Virol. **61(5)**:1639-1646 (1987)].

Temin is described *supra*. In addition, Temin teaches that the vectors may employ splice donor and acceptor sites. See page 16, construct 5. Bender et al. teaches that the packaging signal of vectors based on the Moloney murine leukemia virus extends into the *gag* region. Applicant claims vectors in which a splice donor and a splice acceptor site are included, as well as an additional portion of the *gag* gene to enhance packaging. The combined teachings of the prior art would have suggested such modifications to known vectors in the art as a means of regulating gene expression and increasing efficiency of vector packaging.

Claims 5, 6 and 20 are rejected under 35 U.S.C. § 103 as being unpatentable over Temin [in *Gene Transfer*, R. Kucherlapati (Ed.), Plenum Press, N.Y., pp. 149-187, (1986)] and Bender et al. [J. Virol. **61(5)**:1639-1646 (1987)] as applied to claims 2, 3, 4 and 20 above, and further in view of Cone et al. [Proc. Natl. Acad. Sci. USA **81**:6349-6353 (1984)].

Cone et al. teach the construction and use of helper-free recombinant retroviral vectors. Although the vector pZipNeoSV(X)1 used contains a selectable marker, as noted on page 6353:

> ...one can readily isolate lines such as ψ-AM2275 that produce $> 10^5$ recombinant virus per ml. These titers are high enough to facilitate the nonselective introduction of genes into 100% of a population of cells at high enough cell numbers to allow rapid analysis of DNA, RNA, or protein.

Applicant further claims recombinant retroviral vectors in which the vectors do not contain a [gene encoding a] selectable marker. Such constructs would have been obvious given the combined teachings of the prior art suggesting that packaged vectors at sufficient titers can be used to transfer genes non-selectively. The ability to generate high titer vectors would have suggested to the skilled artisan that inclusion of a gene encoding a selectable marker would not be necessary in these circumstances.

Claims 9 and 20 are rejected under 35 U.S.C. § 103 as being unpatentable over Temin [in *Gene Transfer*, R. Kucherlapati (Ed.), Plenum Press, N.Y., pp. 149-187, (1986)] taken in view of either of Kenten et al. [WO 86/05807] or Kuo et al. [European Pat. Application 0 150 735 A2]

Temin is described *supra.*

Kenten et al. describes the construction of various plasmid vectors for expression of foreign genes in myeloma cell lines. This reference demonstrates the vector-mediated transfer of the gene for tissue plasminogen activator (tPA) under the control of a retroviral LTR promoter into mammalian cells.

Kuo et al. describes the cloning and expression in *E. coli* of Factor VIIIC. At page 34 the transfer of the gene into mammalian cells by way of retroviral vectors is suggested.

Applicants claim retroviral vectors expressing factor VIII or tPA. The combined teachings of the prior art suggest the usefulness of expression of these proteins in mammalian cells in culture. The prior art of either Kenten et al. or Kuo et al. suggest expression of such genes by vector mediated gene transfer. The use of retroviral vectors would have been obvious, especially give the suggestions of Kenten et al. or Kuo et al. to use retroviral LTRs as promoters.

Claims 10, 11, 17, 18 and 20 are rejected under 35 U.S.C. § 103 as being unpatentable over Temin [in *Gene Transfer*, R. Kucherlapati (Ed.), Plenum Press, N.Y., pp. 149-187, (1986)] and Emerman et al. [J. Virol. **50(1)**:42-49 (1984)].

Temin is described *supra*.

Emerman et al. describe the construction of retroviral vectors in which an internal heterologous α-globin promoter and 5' untranslated region is used to express the heterologous thymidine kinase gene.

Applicants claim recombinant retroviral vectors which contain the α-globin promoter and 5' untranslated region. Emerman et al. teach the use of such a promoter construct to express a heterologous gene from retroviral vectors. It would have been obvious to use such promoter constructs in the vectors of Temin et al. given the combined teachings of the prior art.

Claims 16 and 20 are rejected under 35 U.S.C. § 103 as being unpatentable over Temin

[in *Gene Transfer*, R. Kucherlapati (Ed.), Plenum Press, N.Y., pp. 149-187, (1986)] and Emerman et al. [J. Virol. **50(1)**:42-49 (1984)] as applied to claims 10, 11, 17, 18 and 20 above, and further in view of Yee et al. [Proc. Natl. Acad. Sci. USA **84**:5197-5201 (1987)] or Yu et al. [Proc. Natl. Acad. Sci. USA **83**:3194-3198 (1986)].

Temin and Emerman et al. are described *supra*.

Yee et al. and Yu et al. describe the modification of retroviral vectors for the purpose of deleting the 3'LTR enhancer or promoter sequences. These vectors are termed "disabled retroviral vectors" or "self-inactivating retroviral vectors". The intent is to prevent the activation of downstream genes by the 3'LTR when the retrovirus inserts into the host genome. Or, the inactivated elements may transfer to the 5'LTR, inactivating the enhancer in the 5'LTR, and thereby allow regulated expression of a heterologous gene from an internal promoter, without interference by expression from an active 5'LTR.

Applicants are claiming further modifications of the retroviral vectors of the instant application such that the retroviral enhancer element is inactivated such that the α-globin gene promoter controls the expression of the inserted heterologous gene. Given the combined teachings of the prior art, inactivation of the retroviral enhancer would have been obvious for allowing specific expression through the heterologous promoter.

Claim 19 is rejected under 35 U.S.C. § 103 as being unpatentable over Temin [in *Gene Transfer*, R. Kucherlapati (Ed.), Plenum Press, N.Y., pp. 149-187, (1986)] and Emerman et al. [J. Virol. **50(1)**:42-49 (1984)] as applied to claims 10, 11, 17, 18 and 20 above, and further in

view of Kenten et al. [WO 86/05807] or Kuo et al. [European Pat. Application 0 150 735 A2].

Temin, Emerman et al., Kenten et al., and Kuo et al. are described *supra*.

Applicant further claims retroviral vectors which express either factor VIII or tPA. For essentially the same reasons as set forth hereinabove, the combined teachings of the prior art teaches the importance of expressing these proteins. It would have been obvious to express either factor VIII or tPA by way of such retroviral vectors.

Claims 12-15, 20 and 22 are rejected under 35 U.S.C. § 103 as being unpatentable over Temin [in *Gene Transfer*, R. Kucherlapati (Ed.), Plenum Press, N.Y., pp. 149-187, (1986)] and Emerman et al. [J. Virol. **50(1)**:42-49 (1984)] as applied to claims 10, 11, 17, 18 and 20 above, and further in view of Anderson [Science **226**:401-409 (1984)] and deVilliers [U.S. Patent 4,963,481].

Anderson describes retroviral vector for expression of exogenous genes. On pages 405-407. methods for optimizing and modifying the expression of exogenous genes is noted. In particular, the use of exogenous enhancers is described therein.

deVilliers et al. describe in column 1, lines 32-53 the use of enhancers, specifically the CMV enhancer, to optimize expression of exogenous genes inserted into vectors.

Applicant further claims retroviral vectors in which an exogenous enhancer is included to express heterologous genes. The combined teachings of the prior art suggest the use of exogenous enhancers, in particular the CMV enhancer, for this same purpose. It would have been obvious to include such enhancers for this purpose.

Claim 22 is rejected under 35 U.S.C. § 103 as being unpatentable over Temin [in *Gene Transfer*, R. Kucherlapati (Ed.), Plenum Press, N.Y., pp. 149-187, (1986)] taken in view of Anderson [Science **226**:401-409 (1984)] or deVilliers [U.S. Patent 4,963,481].

Temin, Anderson and deVilliers are described *supra*.

Applicant claims a defective recombinant retroviral vector based on a murine leukemia virus, wherein the vector contains an exogenous enhancer. For the reasons as set forth hereinabove, the use of exogenous enhancers as suggested by Anderson or deVilliers in the vectors of Temin would have been obvious.

Claims 23 and 24 are rejected under 35 U.S.C. § 103 as being unpatentable over Temin [in *Gene Transfer*, R. Kucherlapati (Ed.), Plenum Press, N.Y., pp. 149-187, (1986)], Anderson [Science **226**:401-409 (1984)] and deVilliers [U.S. Patent 4,963,481] taken in view of either of Hilberg et al. [Proc. Natl. Acad. Sci. USA **84**:5232-5236 (1987)] or Holland et al. [Proc. Natl. Acad. Sci. USA **84**:8662-8666 (1987)].

Temin, Anderson, deVilliers, Hilberg et al. and Holland et al. are described *supra*. Applicant is claiming retroviral vectors in which the exogenous enhancer is from myeloproliferative sarcoma virus (MPSV) (claim 23) or from Moloney Friend virus (claim 24). Given the combined teachings of the prior art, substitution of either enhancer for the exogenous enhancer suggested by Anderson or deVilliers would have been obvious. This would have been obvious in view of the teaching that the MPSV enhancer allows expression of the viral vector genome in embryonal carcinoma cells, a developmental cell line, while the (Fr-MuLV) enhancer

allows expression of the viral vector genome in hematopoietic progenitor cells.

Claims 25-31 are rejected under 35 U.S.C. § 103 as being unpatentable over Temin [in *Gene Transfer*, R. Kucherlapati (Ed.), Plenum Press, N.Y., pp. 149-187, (1986)], Anderson [Science **226**:401-409 (1984)] and deVilliers [U.S. Patent 4,963,481] taken in view of either of Hilberg et al. [Proc. Natl. Acad. Sci. USA **84**:5232-5236 (1987)] or Holland et al. [Proc. Natl. Acad. Sci. USA **84**:8662-8666 (1987)] as applied to claims 23 and 24 above, and further in view of either Franz et al. [Proc. Natl. Acad. Sci. USA **83**:3292-3296 (1986)] or Weiher et al. [Journal of Virology **61(9)**:2742-2746 (1986)].

Temin, Anderson, deVilliers, Hilberg et al., Holland et al., Weiher et al. and Franz et al. are described *supra*. Applicant is claiming retroviral vectors in which the vectors either comprise the B2 mutation, or comprise LTRs derived from the MPSV. As noted hereinabove, such vectors would have been obvious given the combined teachings of the prior art. The B2 mutation of MuLV vectors works synergistically with the enhancer element and allows for enhanced RNA stability in certain cells, such as F9 cells. The discussion in Weiher et al. suggests that the B2 mutation may affect the efficiency of translation as well. Inclusion of the B2 mutation in the vectors as claimed would have been obvious as a means of increasing gene expression in these vectors. Franz et al. teach that retroviral vectors using MPSV LTRs can result in expanded host range of the vectors, especially in efficient transduction of embryonic cells. Inclusion of these LTR elements would have been obvious as a means of increasing the host range of the MuLV based vectors.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention.

The specification at page 10, lines 27-28 fails to provide an adequate written description of Figure 11. All of the blocks shown in this section are meant to designate a part of the vector construct, yet each block is empty. The specification notes vectors α-SGC and α-G-SGC. It is unclear what the difference is between these vectors. Compare page 47, lines 31-34 and page 30, beginning at line 11. Also, it is unclear at page 44, line 21 how the α-SGC-LacZ vector is "improved" over the α-SGC vector. Does the inclusion of the *lacZ* gene result in the improvement?

The specification on pages 59 and 60 notes the deposit of applicant's constructs designated ATCC accession Nos. 68726, 68727, 68728, 68729, 68754 and 68755. In addition, it is noted that the unrestricted availability of the deposited strains upon issuance of the pertinent U.S. patent is noted at page 60. These deposits are necessary to provide an enabled disclosure of the invention as claimed under 35 U.S.C. § 112, first paragraph.

Claims 1-31 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

Claims 1-6, 8-11, 15, 17-21 and 24 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claims 1 and 21, how are the elements arranged? What comprises an "operable combination"?

Regarding claim 2, it is unclear what comprises a "portion" of a *gag* coding region and where is that "portion" located in the vector?

Regarding claim 3, the claim is drawn to a splice site "located upstream from said gene of interest". This claim is also dependent upon claims 2 and 1, which do not have a "gene of interest" but rather "**an insertion site** for a gene of interest". As such, the claim as written is incorrect.

Regarding claim 4, what comprises a "*gag* transcriptional promoter"? Is this the 5'LTR?

Regarding claim 5, the vector does not contain a selectable marker, but rather contains a **gene encoding** a selectable marker.

Regarding claims 6 and 15, the vector must have **all** of the identifying characteristics of the ATCC deposit claimed. Unless the vector has all of these characteristics it is not necessarily identical to the deposited vector.

Claims 8 and 18 contain improper Markush groups. Applicant's vectors express proteins. Are these protein hormones and drugs being expressed? The term "drug" is vague and indefinite. The term "drug" has other established meanings in the art, so consequently

applicant's usage of the term is confusing.

Claims 9 and 19 are incorrect as written. The gene is not factor VIII or tPA, but rather the gene **encodes** factor VIII or **encodes** tPA.

Regarding claim 10, how is the alpha globin transcriptional promoter present in the vector of claim 1? The elements are not set forth clearly so that the skilled artisan can determine exactly where or how the promoter is present in the vector. The location of this promoter in the vector, i.e. direction of transcription from it, might affect its function.

Regarding claim 11, applicant should use consistent designations for the terms instead of stating both α-globin and alpha-globin in the claim.

Regarding claim 17, how is the inserted gene expressed? The elements of the claim are not clearly stated. Expression depends upon the insertion site. Therefore, it cannot be determined if the gene is under transcriptional control of the 5'LTR or the alpha globin promoter.

Regarding claim 20, this claim is improper as it refers to two claims in the conjunctive rather than in the alternative. See MPEP 608.01(n) and 37 CFR § 1.75(c).

Regarding claim 21, there is a period (.) in the middle of the claim following the term *env*.

Regarding claim 24, the term is Moloney, not Molony.

The oath or declaration is defective. A new oath or declaration in compliance with 37 C.F.R. § 1.67(a) identifying this application by its Serial Number and filing date is required.

See M.P.E.P. §§ 602.01 and 602.02.

The oath or declaration is defective because:

It does not include the date of execution. A new oath will not be required if a certificate from the notary giving the actual date when the oath was made is supplied.

Specifically, the inventors Lori F. Rafield and Paul Robbins failed to provide the date that oath was executed.

Papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Art Unit 1804 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number for Art Unit 1804 is (703) 308-0294.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. F. Railey, whose telephone number is (703) 308-0281. The examiner can normally be reached on Monday-Thursday from 7:30 AM-6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jacqueline Stone, can be reached at (703) 308-3153. The fax phone number for Art Unit 1804 is (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Jasemine C. Chambers

JASEMINE C. CHAMBERS
PRIMARY EXAMINER
GROUP 1800

Johnny F. Railey II, Ph.D.
August 1, 1995